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Influence of chronic inflammation and autoimmunity on coronary calcifications and myocardial perfusion defects in systemic lupus erythematosus patients

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Abstract
Objective Conventional risk factors for coronary artery disease fail to explain the increased frequency or cardiovascular morbidity in systemic lupus erythematosus (SLE) patients. This study was conducted to determine the possible influence of autoimmune and inflammatory phenomena markers on coronary artery calcifications and myocardial perfusion abnormalities in SLE patients.
Materials and methods Multi-detector computed tomography (MDCT)-based coronary calcium scoring and single photon emission computerized tomography (SPECT) studies (Tc-99m sestamibi) were performed in 60 SLE patients in stable clinical condition, without a prior history of coronary artery disease. Laboratory evaluation included serum C-reactive protein (CRP), complement C3c and C4 components and antiphospholipid antibodies (aPL). The latter included anticardiolipin (aCL) and anti-β2-glycoprotein I (aβ2GPI) antibodies, of both IgG and IgM classes, and lupus anticoagulant (LA) in plasma.
Results SPECT revealed persistent perfusion defects in 22 (36.7%) patients and exercise-induced defects in eight (13.3%), while MDCT revealed coronary calcifications in 15 (25%). Calcium scores ranged from 1 to 843.2 (mean 113.5 ± 259.7). No association was found between conventional coronary artery disease risk factors (obesity, hypertension, tobacco use, hyperlipidaemia, diabetes) nor CRP, C3c or C4 levels and coronary calcifications or myocardial perfusion defects. On the contrary, in patients with these pathologies, augmented autoimmunization was found, reflected by increased aCL IgG and antiβ2GPI IgG levels. In patients with aCL IgG >20 RU/ml or antiβ2GPI IgG >3 RU/ml, the relative risk of coronary calcification formation was 4.1 compared to patients with normal values. Accordingly, in LA-positive patients the relative risk of coronary calcification formation was 4.4 compared to LA-negative patients.
Conclusions Conventional risk factors for coronary artery disease as well as markers of an ongoing inflammation did not show any association with perfusion defects and/or coronary artery calcifications in SLE patients. On the contrary, calcified atherosclerotic plaques and myocardial perfusion defects were observed mainly in patients with elevated levels of anticardiolipin and aβ2GPI antibodies of the IgG class. It might be speculated that coronary artery calcifications and perfusion defects are a result of antiphospholipid antibodies-induced coronary artery microthrombosis.

Keywords Systemic lupus erythematosus · Autoimmune diseases · Coronary calcification · Atherosclerosis · MDCT · SPECT · Perfusion scintigraphy

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Introduction

Objectives

Systemic lupus erythematosus (SLE) is a generalized autoimmune disease, in which a diffuse, chronic inflammatory reaction plays an important etiological role. Nowadays, the mortality of SLE patients is influenced by increased occurrence of severe cardiovascular complications [1].

Conventional risk factors for coronary artery disease (diabetes, hypertension, tobacco use, hyperlipidaemia, sedentary lifestyle) do not explain the increased risk of atherosclerosis and cardiovascular complications in SLE patients [2]. The other possible mechanisms include a generalized, chronic inflammation, reflected by high C-reactive protein (CRP) level. The relation between the increased CRP level and life-threatening cardiovascular episodes is well documented [2]. The other characteristic finding in generalized inflammation is a reduced level of complement system components (mainly C3c and C4).

Beside the chronic inflammation, the second factor that may potentially influence pathologic changes in the arteries is the presence of antiphospholipid antibodies (aPL). Elevated aPL levels are related to an increased risk of thrombosis in the arteries and microcirculation [3–7]. The coexistence of aPL and thrombosis in the above-mentioned vascular beds meets the criteria for the diagnosis of antiphospholipid syndrome [8], which appears in one-third of SLE patients [9].

Aim of the study

This study was conducted to determine the influence of chronic inflammation and the presence of aPL on coronary artery calcifications and myocardial perfusion abnormalities in SLE patients assessed by multi-detector computed tomography (MDCT)-based coronary calcium scoring and single photon emission computed tomography (SPECT).

Methods

Inclusion and exclusion criteria

The study was performed in 60 consecutive patients treated for systemic SLE in the Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland. All patients fulfilled at least four American College of Rheumatology classification criteria for SLE [10, 11]. Before the study, informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by the Ethical Committee of the Jagiellonian University in Krakow.

Inclusion criteria comprised stable clinical conditions of SLE (no need for immunosuppressive therapy intensification, i.e. current immunosuppressive drug dose increase or introduction of an additional immunosuppressive drug within the last 3 months). Exclusion criteria were as follows: prior history of coronary artery disease, known cancer, clinical symptoms of heart failure (NYHA III or IV class), renal failure (creatinine clearance <30 ml/min) and/or respiratory failure.

Patients studied

In the group of 60 patients examined, 54 (90%) were females andsix(10%) males, aged 20–73 years (mean age 51.8 years). The duration of the disease at the time of examination was between 2 and 32 years (mean 15.5 years). Three patients had been previously diagnosed with antiphospholipid syndrome (APS) based on the revised APS classification criteria [8]. One of the three suffered from an objectively confirmed pulmonary embolism. There were two tobacco smokers; none of the patients was obese. The history revealed arterial hypertension in three subjects; there were no diabetic patients. ECG recordings at rest were normal in all the patients. The results of peripheral blood count, serum sodium, potassium, glucose, creatinine and urinalysis were all normal. The distribution of the patients according to their SLEDAI score [12] is shown in Table 1. The main complaints at inclusion were arthralgias and, among laboratory findings, low complement levels and increased ANA titers (see below). The immunosuppressive treatment included methylprednisolone in 32 (53.3%) subjects (≤4 mg for clinical stability maintenance), prednisone in two (3.3%), chloroquine derivate in five (8.3%), azathioprine in four (6.7%), cyclophosphamide in three (5%), and methotrexate in two (3.3%). The remaining patients had not used any immunosuppressive drugs in the last 12 months of observation. Other treatment included angiotensin-converting enzyme inhibitors in four (6.7%) subjects, beta-blockers in three (5%) and calcium channel blockers in two (3.3%). APS patients were treated with anticoagulant (warfarin, two patients) or antiplatelet therapy (aspirin, one patient).

The presence and types of autoantibodies identified in the patients examined as well as the concentrations of CRP and complement C3c and C4 components are shown in Table 2.

Table 1 SLEDAI score in SLE patients at the time of study

SLEDAI score	Number of patients (%)
0	1 (1.7)
2	18 (30.0)
4	18 (30.0)
5	7 (11.7)
6	6 (10.0)
8	6 (10.0)
9	1 (1.7)
10	1 (1.7)
12	1 (1.7)
20	1 (1.7)

SPECT study

In all the patients SPECT studies (ECAM Gamma Camera, Siemens, Germany) were performed at rest and during exercise in a 2-day protocol. On the first day, at near maximal stress, a 25–40 mCi dose of Tc-99m sestamibi was injected (the actual dose was modified taking into account the patient's weight) and the exercise was continued forone additional minute after the injection. Tc-99m sestamibi SPECT imaging was begun 15–30 min later. On the second day, rest examinations were performed. SPECT was performed using a circular 180° acquisition for 60 projections at 20 s per projection. Myocardial perfusion was assessed in 17 left ventricle myocardial segments. The number of segments with persistent or exercise-induced perfusion defects were assessed visually by analysts blinded to any other information.

Coronary calcium scoring

Coronary calcium scoring was performed using a multidetector CT imager (Somatom Definition, Siemens, Germany). The images were ECG-triggered with 3-mm-thick sections obtained covering the whole heart. Coronary artery calcifications were defined as lesions with attenuation greater than 130 HU in more than four adjacent pixels. In order to quantify coronary calcium, 3D Leonardo application (Siemens, Germany) was used. The number of atherosclerotic plaques in particular coronary arteries and their volume were assessed. The Agatson calcium score was calculated [13].

Laboratory tests

Standard laboratory tests were performed. Additionally, the levels of CRP (high-sensitivity) and complement system C3c and C4 factors were assessed by nephelometry (Siemens, Germany).

Serum levels of anticardiolipin (aCL) and anti-β2-glycoprotein I (aβ2GPI) antibodies (of both IgG and IgM classes) were measured using a home-made ELISA with Sapporo standard for antiβ2GPI antibody measurements (HCAL for IgG, EY2C9 for IgM) [9]. The values exceeding the 99th percentile of a healthy population sample were considered positive.

Lupus anticoagulant (LA) determination was performed in accordance with the three-step procedure recommended by the International Society on Thrombosis and Haemostasis [14].

Statistical analysis

Statistical analysis was performed using Statistica Six Sigma software. All numerical data were expressed as mean values ± standard deviations or as proportions. Continuous variables were compared using the t test. The chi-square test was used to examine differences in proportions. The level for statistical significance was predetermined at $p < 0.05$. To adjust for the confounding

Table 2 Autoantibodies and other laboratory parameters measured in SLE patients studied

	Range (mean ± SD)	Number of patients with out-of-range levels (%)
aCL IgG [RU/ml]	0.68–121.56 (14.4 ± 20.3)	20 (33.3)
aCL IgM [RU/ml]	1.62–52.93 (12.1 ± 10.6)	26 (43.3)
antiβ2GPI IgG [RU/ml]	0.16–95.33 (3.8 ± 15.3)	8 (13.3)
antiβ2GPI IgM [RU/ml]	0.14–21.66 (2.2 ± 3.7)	24 (40)
LA	–	11 (18.3)
ANA [titer]	0–1/20,480	56 (93.3)
CRP [mg/l]	0.18–41.70 (4.16 ± 7.40)	11 (18.3)
C3c [g/l]	0.43–1.39 (0.90 ± 0.25)	32 (53.3)
C4 [g/l]	0.02–0.26 (0.13 ± 0.05)	16 (26.7)

aCL Anticardiolipin antibodies (cut-off value for IgG >20 RU/ml, for IgM >30 RU/ml; see "Methods"), *antiβ2GPI* antiβ2-glycoprotein I antibodies (cut-off value for IgG >3 RU/ml, for IgM >2.6 RU/ml; see "Methods"), *LA* lupus anticoagulant, *ANA* antinuclear antibodies, *CRP* C-reactive protein. Elevated value for CRP >5 mg/l. Decreased values for C3c <0.9 g/l, for C4 <0.1 g/l

effect of age on SPECT and MDCT results, an ANOVA model was used with age as a covariate.

Results

In 37 (61.6%) out of 60 patients examined, pathologic results of SPECT or MDCT studies were found. Figure 1 shows examples of coronary calcifications and myocardial perfusion defect observed in a patient with elevated aPL levels.

SPECT study revealed myocardial perfusion abnormalities in 30 (50.0%) patients: persistent defects in 22 (36.7%) patients, exercise-induced defects in 8 (13.3%). The distribution of patients according to the number of underperfused myocardial segments of the left ventricle is shown in Table 3. Out of 30 patients with perfusion abnormalities, in 21 (70% of this group) classic signs of ischaemia (horizontal or down-slope ST depression ≥0.1 mV) were visible in ECG recordings during exercise.

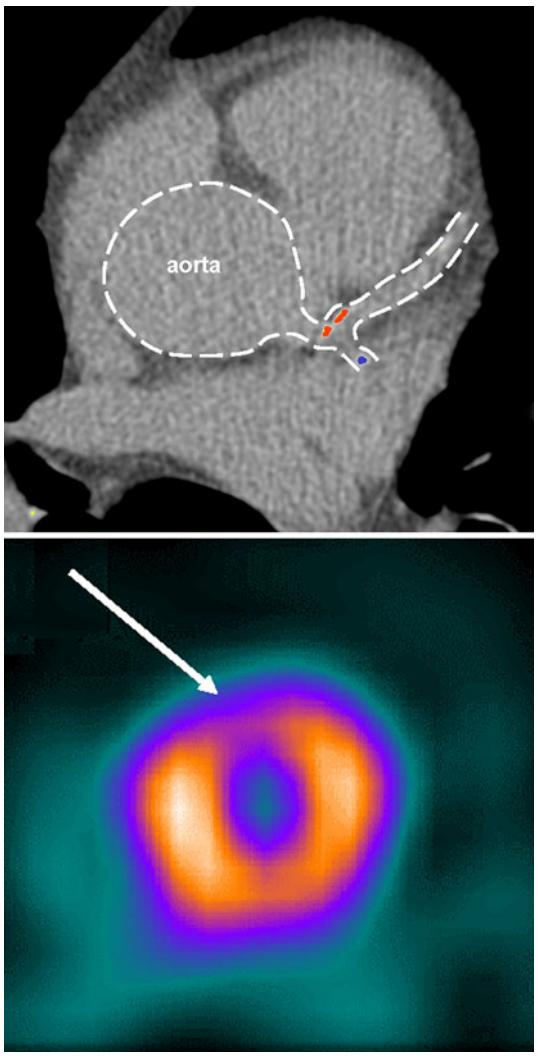

Fig. 1 Examples of MDCT (*above*) and SPECT (*below*) results in a patient with elevated aCL IgG (26.11 RU/ml), elevated antiβ2GPI IgG (3.66 RU/ml) and positive lupus anticoagulant test

Table 3 The distribution of SLE patients according to the number of myocardial segments with perfusion abnormalities in SPECT study

Number of segments with perfusion abnormalities	Persistent defects (%)	Exercise-induced defects (%)
0	38 (63.3)	52 (86.7)
1	–	2 (3.3)
2	7 (11.7)	–
3	13 (21.7)	4 (6.7)
4	–	2 (3.3)
5	2 (3.3)	–
Total	60 (100)	60 (100)

Table 4 The distribution of SLE patients according to perfusion abnormalities and coronary calcifications in particular coronary arteries

Coronary arteries	SPECT (%)	MDCT (%)
LAD	22 (73.3)	8 (53.3)
RCA	3 (10.0)	2 (13.3)
LAD + RCA	3 (10.0)	1 (6.7)
LAD + Cx	2 (6.7)	–
LAD + Cx + RCA	–	4 (26.7)
Total	30 (100)	15 (100)

LAD Left anterior descending artery, *RCA* right coronary artery, *Cx* circumflex artery

MDCT revealed coronary calcifications in 15 (25%) patients. The number of atherosclerotic calcified plaques ranged from 1 to 23 (mean 6 ± 6.9), their volume 2–761.8 (108.8 ± 234.2) mm^3. Calcium scores ranged from 1 to 843.2 (mean 113.5 ± 259.7).

The distribution of patients according to perfusion abnormalities and coronary calcifications in particular coronary arteries is shown in Table 4.

Myocardial perfusion abnormalities together with the presence of coronary calcifications were present in nine (15%) patients. In 21 (35%) patients SPECT study was abnormal despite the lack of coronary calcifications (calcium score = 0). On the other hand, in six (10%) patients with mild calcium deposits [1–3 plaques, calcium score 4.4–35.1 (mean 14.87 ± 14.24)], SPECT study did not show perfusion defects.

We found no influence of conventional risk factors for coronary artery disease (obesity, hypertension, tobacco use, hyperlipidaemia, diabetes) on coronary calcifications formation or myocardial perfusion defects (Tables 5, 6). The generalized inflammation reflected by high CRP and low C3c and C4 levels did not significantly result in the presence of atherosclerotic lesions or perfusion disturbances.

Table 5 Age, glucose and lipid levels, inflammatory and immunologic findings in patients without (calcium score = 0) and with coronary calcifications on MDCT study

	Calcium score = 0 (n = 45)	Calcium score >0 (n = 15)	p
Age (years)	**36.06 ± 11.61**	**48.55 ± 11.56**	**<0.01**
Total cholesterol (mmol/l)	4.93 ± 1.10	5.0 ± 1.42	ns
LDL cholesterol (mmol/l)	2.51 ± 0.51	3.10 ± 1.38	ns
HDL cholesterol (mmol/l)	1.23 ± 0.18	1.38 ± 0.45	ns
Triglycerides (mmol/l)	1.54 ± 0.06	1.56 ± 0.74	ns
Glucose (mmol/l)	4.73 ± 0.23	4.0 ± 0.63	ns
CRP (mg/l)	4.48 ± 8.43	3.23 ± 3.24	ns
C3c (g/l)	0.89 ± 0.23	0.92 ± 0.30	ns
C4 (g/l)	0.14 ± 0.05	0.11 ± 0.06	ns
aCL IgG (RU/ml)	**11.2 ± 10.10**	**24.70 ± 15.91**	**<0.05**
aCL IgM (RU/ml)	11.6 ± 11.30	13.50 ± 9.00	ns
antiβ2GPI IgG (RU/ml)	**1.31 ± 1.18**	**11.61 ± 10.91**	**<0.05**
antiβ2GPI IgM (RU/ml)	2.13 ± 4.10	2.21 ± 2.23	ns
LA (n, %)	**3 (6.7%)**	**8 (53.3%)**	**<0.01**
ANA (titer)	**4668 ± 2717**	**8320 ± 4521**	**<0.05**

CRP C-reactive protein, *aCL* anticardiolipin antibodies, *antiβ2GPI* antiβ2-glycoprotein I antibodies, *LA* lupus anticoagulant, *ANA* antinuclear antibodies

ns not significant. Values in bold type are statistically significant

Table 6 Age, glucose and lipid levels, inflammatory and immunologic findings in patients without myocardial perfusion defects and with perfusion defects on SPECT study

	Normal perfusion (n = 30)	Perfusion defects (n = 30)	p
Age (years)	**34.9 ± 10.92**	**42.75 ± 13.68**	**<0.05**
Total cholesterol (mmol/l)	5.55 ± 2.05	4.7 ± 0.45	ns
LDL cholesterol (mmol/l)	2.86 ± 0.88	3.10 ± 1.57	ns
HDL cholesterol (mmol/l)	1.31 ± 0.51	1.38 ± 0.38	ns
Triglycerides (mmol/l)	1.54 ± 0.61	1.57 ± 0.79	ns
Glucose (mmol/l)	4.8 ± 0.28	4.3 ± 0.42	ns
CRP (mg/l)	5.71 ± 10.07	2.6 ± 2.48	ns
C3c (g/l)	0.91 ± 0.25	0.89 ± 0.26	ns
C4 (g/l)	0.12 ± 0.05	0.13 ± 0.06	ns
aCL IgG (RU/ml)	**11.99 ± 4.66**	**16.03 ± 13.6**	**<0.05**
aCL IgM (RU/ml)	13.11 ± 12.12	11.12 ± 9.12	ns
antiβ2GPI IgG (RU/ml)	**1.31 ± 0.43**	**6.19 ± 6.82**	**<0.05**
antiβ2GPI IgM (RU/ml)	2.12 ± 4.9	2.17 ± 2.02	ns
LA (n, %)	5 (16.7%)	6 (20.0%)	ns
ANA (titer)	4204 ± 4716	6837 ± 7823	ns

CRP C-reactive protein, *aCL* anticardiolipin antibodies, *antiβ2GPI* antiβ2-glycoprotein I antibodies, *LA* lupus anticoagulant, *ANA* antinuclear antibodies

ns not significant. Values in bold type are statistically significant

On the contrary, regardless of their age, in patients with atherosclerotic plaques in coronary vessels or with myocardial perfusion defects, augmented autoimmunization was found, reflected as increased aCL IgG and antiβ2GPI IgG levels (Tables 5, 6). Additionally, in patients with coronary calcifications a significantly higher level of antinuclear antibodies and higher frequency of lupus anticoagulant incidence were observed (Table 5).

In all three patients with APS, perfusion defects were observed on SPECT study, and in two of them coronary atherosclerotic plaques were present.

In patients with elevated levels of aCL IgG >20 RU/ml or antiβ2GPI IgG >3 RU/ml, the relative risk of coronary calcification formation was 4.1 compared to patients with normal values. Accordingly, in patients positive for lupus anticoagulant, the relative risk of coronary calcification formation was 4.4 compared to LA-negative patients.

Discussion

The major findings of this study include the association of coronary calcification formation and myocardial perfusion abnormalities in SLE patients with the presence of antiphospholipid antibodies. Neither conventional coronary artery disease risk factors (obesity, hypertension, tobacco use, hyperlipidaemia, diabetes) nor CRP, C3c and C4

levels revealed a significant influence on these pathologies in the studied population.

Our results support the data previously published showing the high frequency of myocardial perfusion defects in SLE patients [15, 16]. Perfusion defects were present in 50% of cases, despite normal rest ECG recordings and lack of myocardial ischaemia clinical symptoms. In most of our patients the number of left ventricle underperfused segments was low (2–3). It has to be stressed, however, that even small perfusion defects in SPECT strongly affect the prognosis in non-SLE populations [17, 18]. We showed a higher frequency of persistent perfusion abnormalities compared to exercise-induced defects. This might be partially explained by the fact that antiphospholipid antibodies are associated with thrombotic events in coronary microcirculation [19], which is discussed below. Thrombosis in microcirculation might lead to the small persistent perfusion defects observed in our study, whereas exercise-induced defects, usually observed in coronary artery disease, are caused by the presence of atherosclerotic plaques narrowing the epicardial arteries.

Besides the presence of myocardial perfusion abnormalities, 25% of our asymptomatic SLE patients manifested atherosclerosis in coronary arteries. Coronary vessels are most frequently affected by calcifications; in a recently published study of 50 SLE patients [20], the frequency of atherosclerotic plaques observed in MDCT was highest in coronary arteries (42% of patients with calcifications), followed by carotid arteries (24% of patients with calcifications). In accordance with our findings, a study of 157 SLE patients showed that in young subjects with the mean age of 40, the frequency of coronary artery calcifications is 30–40% [21]. This percentage is relatively higher than in the general population: in a study of 35,388 subjects calcium scores >10 were observed in only 10% of cases, and calcium scores >100 in 2% [22]. Coronary calcium deposits provide independent prediction of short- and long-term cardiac events [23–25]. Even in patients with normal SPECT results, the increased coronary calcium score identifies subjects at high long-term cardiac risk [23].

Interestingly, our study did not show an influence of conventional risk factors of coronary artery disease (obesity, hypertension, tobacco use, hyperlipidaemia, diabetes) on coronary calcification formation or myocardial perfusion defects. Moreover, a generalized inflammation reflected by higher CRP and lower C3c and C4 concentrations did not significantly result in the presence of atherosclerotic lesions. This may be due to the lack of subjects with severely augmented inflammatory process in our study: in patients with CRP levels >20 mg/l its influence on cardiovascular damage was reported [2].

In patients with myocardial perfusion defects or atherosclerotic plaques in coronary vessels, augmented autoimmunization was found, reflected as an increased aCL IgG and antiβ2GPI IgG levels. The evidence that antiphospholipid autoantibodies play a role in thrombosis is persuasive [3]. Various studies have suggested that these antibodies may cause thrombosis by activation of endothelial cells or platelets or by inhibition of the protein C activation pathway [4–7]. Although antiphospholipid antibodies are associated with arterial and venous thrombosis, the extent to which they influence other clinical manifestations is either controversial or uncertain. The data from the literature based on echocardiography suggest its relation to valvular pathology [26], but in other studies no such relation has been found [27]. There are, however, reports showing higher titers of aCL [28] and antiβ2GPI [29] antibodies in patients with SLE or MCTD and pulmonary hypertension. It is tempting to speculate that perfusion abnormalities results from thrombi formed in the coronary microcirculation leading to perfusion defects in small regions of myocardium. Such defects, localized predominantly in the segments supplied by the left anterior descending artery, were observed in our study.

The antiphospholipid antibodies may also initiate or exacerbate the process of lipid deposition and plaque formation [30]. Among antiphospholipid antibodies, a crucial role in the pathogenesis of atherosclerosis is attributed to aCL antibodies and antiβ2GPI antibodies [31, 32].

Increased levels of antinuclear antibodies in patients with coronary calcifications were also shown in our study. There is little data concerning atherogenesis enhancement by these antibodies. One in-vitro study [33] showed that immune complexes consisting of anti-dsDNA, DNA and LDL augmented cholesterol accumulation in vascular smooth muscle cells and demonstrated cytotoxic activity. It was also reported that determination of antinuclear antibodies may be helpful also in the evaluation of coronary artery disease risk in subjects in whom no generalized autoimmune disease has been diagnosed [34].

Based on the positive results of SPECT and MDCT studies in a high proportion of stable SLE patients without cardiac symptoms, the question of final cardiac diagnosis arises. MDCT is characterized by very high specificity (95–97%) and excellent negative predictive value (93–99%) for stable coronary artery disease diagnosis [35]. The specificity of SPECT is estimated to be 70–75% [35]. Thus, an early stage of coronary artery disease may be diagnosed in patients with atherosclerotic plaques detected by MDCT in our study, as well as in patients with positive SPECT results, reflecting rather a “small vessel” type of the disease.

Our results discussed above may have valuable implications for the management of SLE patients in the future. The presence of atherosclerotic plaques and myocardial perfusion defects on SPECT study are strong predictors of

death [17, 18, 23–25]. The mechanism of formation of these abnormalities, in which microthrombosis might play a major role, should direct our attention to thrombosis prevention in aPL-positive patients. It was reported that in asymptomatic aCL-positive patients thrombo-prophylaxis with aspirin or low-molecular-weight heparin during high-risk periods (surgery, immobilization) is effective in reducing thrombotic complications [36]. Among asymptomatic aCL-positive SLE patients, primary prophylaxis with aspirin and hydroxychloroquine also reduced the frequency of thrombotic events [37]. The value of antithrombotic treatment on perfusion abnormalities and formation of coronary calcifications and, consequently, on the prognosis of aCL-positive SLE patients should be addressed in large prospective clinical trials. It should be emphasized that the value of statin treatment in SLE patients free from clinical symptoms of cardiovascular disease has become an objective of ongoing randomized studies [38].

Conclusion

Coronary calcified plaques and myocardial perfusion defects are present in a high proportion of stable SLE patients without cardiac symptoms. Conventional risk factors for coronary artery disease as well as markers of an ongoing inflammation do not show an association with these pathologies. On the contrary, atherosclerosis is augmented in patients with increased levels of antiphospholipid antibodies of IgG class. It might be speculated that coronary artery calcifications and perfusion defects are a result of coronary artery microthrombosis induced by antiphospholipid antibodies.

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